REMARKS

Reconsideration is requested.

Claim 1-68, 71-72, 75, 77-86, 91-94 and 98-101 have been canceled, without prejudice.

Claims 69-70 73, 74, 76, 87-90, 95-97 and 102 are pending. Claim 95-97 are indicated as being free of the art and are objected to as depending from rejected claims. See page 5 of the Office Action dated November 22, 2006.

The Office Action of November 22, 2006 is understood to contain the following rejections of the noted claims:

(1) Claims 76 and 87 have been rejected as allegedly being anticipated by Hsu (Hepatology, May 1993, Vol. 17, No. 5, pp 763-771),

(2) Claims 68-70, 73, 74, 76, 87-90 and 102 have been rejected as allegedly having been obvious over the combination of

Hsu (Hepatology, May 1993, Vol. 17, No. 5, pp 763-771),

Ralston (WO 92/08734A1),

Tartaglia (Virology 1992, Vol. 188 (1), pp 217-232),

Sutter (PNAS, 1992, Vol. 89, pp 10847-10851), and

Vandenbroeck (European Journal of Biochemistry 1993, Vol. 217, pp 45-52).

The Examiner is requested to advise the undersigned in the event any further rejection or objection to the claims and/or specification are contained in the Office Action of November 22, 2006.

A copy of the applicants priority document EP 94870132.1, filed July 29, 1994 was submitted September 8, 2006. The Examiner is requested to confirm receipt of the same in her next Action.

The Section 102 rejection of claims 76 and 87 over Hsu (Hepatology, May 1993, Vol. 17, No. 5, pp 763-771), is obviated by the above amendments. Hsu fails to teach or suggest the presently claimed recombinant vaccinia vector. Hsu is understood to relate, at best, to a baculovirus vector. Withdrawal of the Section 102 rejection is requested.

The Section 103 rejection of claims 68-70, 73, 74, 76, 87-90 and 102 over the combination of Hsu (Hepatology, May 1993, Vol. 17, No. 5, pp 763-771), Ralston (WO 92/08734A1), Tartaglia (Virology 1992, Vol. 188 (1), pp 217-232), Sutter (PNAS, 1992, Vol. 89, pp 10847-10851), and Vandenbroeck (European Journal of Biochemistry 1993, Vol. 217, pp 45-52) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to appreciate that Hsu teach expression of a particular E1 construct in a baculovirus vector and fails to teach use of vaccinia viral vectors. See pages 2-3 of the Office Action dated November 22, 2006 relating to the Section 102 rejection based on Hsu and page 4, lines 3-4 of the Office Action.

A teaching of expression of an E1 construct in a baculovirus vector fails to teach or suggest or motivate one of ordinary skill in the art to using vaccinia vectors for E1 expression. More importantly, Hsu would have motivated one of ordinary skill in the art away from using vaccinia vectors.

As for Ralston (WO92/08734), the Examiner will apparently accept the fact that the vaccinia constructs taught by the reference are not the same as the currently claimed vaccinia constructs, as the previous Section 102 rejection based on Ralston has been withdrawn.

Ralston includes the following disclosure (spanning pages 10-11 of Ralston (emphasis added)):

> "Additionally, it may be advantageous to express a truncated form of the envelope protein. Both E1 and E2 appear to have a highly hydrophobic domain, which apparently anchors the protein within the endoplasmic reticulum and prevents efficient release. Thus, one may wish to delete portions of the sequence found in one or more of the regions aa170-190, aa260-290 or aa330-380 of E1 (numbering from the beginning of the polyprotein), and aa660-830 of E2 (see for example Figure 20-1 of EP 388,232). It is likely that at least one of these hydrophobic domains forms a transmembrane region which is not essential for antigenicity of the protein, and which may thus be deleted without detrimental effect. The best region to delete may be determined by conducting a small number of deletion experiments within the skill of one of the ordinary practitioner. Deletion of the hydrophobic 3' end of E2 results in secretion of a portion of the E2 expressed, with sialyation of the secreted protein."

Ralston's teaching that

> "one may wish to delete portions of the sequence found in one or more of the regions aa170-190, aa260-290 or aa330-380 of E1" (page 11)

will be understood by one of ordinary skill in the art to be internal deletions of hydrophobic domains. Claim 70, which is dependent on claim 69, requires that the 1st hydrophobic domain of E1 should be present, i.e., not deleted.

As has been previously explained (see Amendment of August 30, 2004), the boundary "285" is described in the application where the 1st hydrophobic domain is described as the domain of the envelope region between positions 264 to 293, plus or minus 8 amino acids (previous claim 70; lines 11-13 on page 18). To include the hydrophobic domain the envelope region should end at position 293, plus or minus 8 amino acids. Subtracting 8 from 293 yields 285. The boundary "285" thus is supported by the description. The boundary "326" is supported by line 11 on page 18 of the description.

Moreover, Ralston did not teach or suggest the importance, nor do they provide any guidance thereto, of the outer boundaries of the HCV E1 protein-encoding part in the expression construct in obtaining efficient HCV E1 protein expression, as is provided by the presently claimed invention.

The Examiner's reliance on Tartaglia is not completely understood and clarification is requested in the event the Examiner continues to rely on the same. Specifically, the reference is understood to teach the construction and properties of a new attenuated vaccinia virus, NYVAC. The only link with protein expression in the cited reference in general can be found in the last sentence of the Discussion section:

> "Furthermore, the use of NYVAC as a **general** laboratory expression vector system may greatly reduce the biological hazards associated with using vaccinia vectors."(emphasis added)

Tartaglia is not believed to teach or disclose how to express the HCV E1 protein efficiently in a vaccinia vector. No general guidance thereto is disclosed, nor does the reference disclose any particular guidance for HCV E1 expression as include in, e.g.,

claim 69 of the current invention. More specifically, Tartaglia do not disclose or suggest a need to define the start- and end-points of the HCV E1 protein-encoding part in the expression constructs between certain boundaries, as required by the presently claimed invention. These particular boundaries are required to obtain efficient HCV E1 protein expression and are nowhere disclosed or suggested by Tartaglia.

The relevance of Tartaglia in relation to HCV E1 expression is not understood. Clarification is requested.

The teachings of Sutter are understood to be similar in nature to the disclosure of Tartaglia with a slightly stronger focus on the usefulness of MVA as an expression vector. Similar to the disclosure of Tartaglia, Sutter fails to teach or suggest the boundaries of the HCV E1 protein-encoding part in the expression constructs of the claims which are particularly important in relation to expression efficiency of the present invention. Moreover, Sutter fails to teach or suggest requirements to obtain efficient HCV E1 protein expression.

The relevance of Vandenbroeck to the cited combination of references and the pending claims is not clear to the applicants. The Examiner's explanation spanning pages 4 and 5 of the Office Action dated November 22, 2006 appears to relate to only claim 74. Clarification however as to the relevance of the document to the cited combination of art and the pending claims is requested in the event a rejection based on the reference is maintained.

The applicants understand Hsu to not teach vectors of the present claims. Moreover, Ralston is understood to disclose vaccinia vectors for expression of HCV envelope proteins. Motivation would not have been provided by Ralston and Hsu to

make the claimed invention. Hsu would apparently have taught away from the teaching of Ralston as well as the claimed invention. Tartaglia or Sutter are understood to disclose, at best, attenuated vaccinia virus strains that may be used for protein expression but do not disclose, teach or suggest HCV envelope protein expression in such vectors. Tartaglia and Sutter therefore are not believed to add anything to Ralston with regard to the subject matter of the pending claims. Vandenbroeck is not believed to cure the deficiencies of the combination of Hsu, Ralston, Tartaglia and Sutter which would not have led one of ordinary skill in the art to have made the presently claimed invention.

The applicants submit, with due respect to the Examiner, that the Examiner appears, from the written record, to misunderstand the claimed invention. The claimed invention, for the first time, exploits the delineation of the boundaries of the HCV E1 protein-encoding part in the expression construct. The boundaries of the claims were not taught or suggested by the cited art and the claimed invention provides unexpected advantages in exploiting these boundaries. The claimed invention and its unexpected advantages provides more than a means of expression of HCV E1 protein in a vaccinia virus vector.

As explained in the Amendment of August 30, 2004, the recombinant vectors of the current invention provide unexpected properties, as disclosed in De Martynoff et al. (Viral Hepatitis and liver disease. Proceedings of IX international symposium on viral hepatitis and liver disease. Rome, Italy, 21-25 April 1996. Edizioni Minerva Medica, Turin 1997, a copy of which was supplied with the Submission of June 7, 2004).

Firstly the Examiner is referred to Table 1 of the present invention (pages 63-64) wherein recombinant vaccinia plasmids and viruses are listed, e.g., pvHCV-11A and pvHCV-10A (4th and 6th plasmid, respectively, in Table 1). Secondly, from Example 2.5 (pages 44-45) it is clear that recombinant vaccinia viruses are named according to the vaccinia recombinant plasmid. Recombinant viruses vvHCV-11A and vvHCV-10A are for example obtained from recombination with plasmids pvHCV-11A and pvHCV-10A, respectively. Referring back to Table 1, the codes of the recombinant vaccinia viruses can thus be easily obtained by exchanging "pv" in the plasmid name for "vv". Nearly all of the recombinant vaccinia viruses schematically provided in Figure 1 on page 220 of De Martynoff et al. (1997) are the same as the ones listed in Table 1 of the present invention. In particular, vvHCV-11A and vvHCV-10A of the current invention are the same as vvHCV-11A and vvHCV-10A listed as the 7th and 9th recombinant vaccinia viruses in Figure 1 of De Martynoff et al. (1997).

De Martynoff et al. (1997) further states in the last sentence of the third paragraph of the left-hand column of page 221:

> "In contrast with constructs encoding single envelope proteins (vvHCV-11A, -10A, -44, Fig.2, lanes 4, 5, 6 and 8), expression levels decreased along with carboxyterminal position of E1 or E2 in polyprotein constructs (vvHCV-33, -65, -66; lanes 3, 8 and 9)."

This illustrates that defining the construct for E1 expression as containing the termination points as presently claimed provides the advantage of increasing E1 expression levels.

The claimed invention would not have been obvious from the combination of cited art applied and withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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